AMENDMENTS TO THE DRAWINGS

Please replace FIG. 13B with the Replacement Sheet for FIG. 13B.

REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 16-24 are pending in the application, and claims 16, 18, 19, and 21-23 are under active consideration. Claims 16-18, 22, and 23 are amended; claims 25-28 are new; and claims 19-21, and 24 are hereby canceled without prejudice to pursuing the canceled subject matter in a continuing application. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the application. Upon entry of these amendments, claims 16-18, 22, 23, and 25-28 will be pending and under active consideration.

b. Amendments to the Claims

Support for the amended claims can be found in the application as originally filed as described below in **Table A**.

Claim	Support
16	Table 1, line 30685; Table 2, lines 1635432, 1635101, 1634771, 1634991, and 1634881; sequence listing; claim 1; and ¶¶ 0045, 0048, 0052, and 0054
17	as described above for claim 16
18	as described above for claim 16
22	as described above for claim 16; ¶¶ 0037, 0046
23	as described above for claim 16; ¶¶ 0037, 0046
25	as described above for claim 16; ¶¶ 0037, 0046
26	as described above for claim 16; ¶¶ 0037
27	as described above for claim 16; ¶¶ 0037
28	as described above for claim 16; ¶¶ 0037

c. Amendments to the Drawings

Figure 13B has been amended to assign a SEQ ID NO to each sequence shown.

d. Amendments to the Specification

Paragraph 0029 is amended to incorporate by reference the replacement sequence listing submitted herewith. Paragraphs 0050 and 0178 are amended to correct a typographical error and remove an embedded hyperlink, respectively. Paragraphs 0073, 0075, 0077, and 0079, which describe Figs. 13B, 14B, 15A, and 16A, D, and E, are amended to assign a SEQ ID NO to the sequences shown in these figures. Paragraphs 0211-0214, and 0235 of pages 117-119, 131, and 132 are amended to assign a SEQ ID NO to each sequence in these paragraphs.

e. Objections to the Application

On pages 3-6 of the Office Action, the Examiner raises objections to the specification and drawings.

(1) Sequence Compliance

On pages 3 and 4 of the Office Action, the Examiner objects to the specification because it allegedly fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825. The Examiner asserts that there are sequences in the specification on pages 117-119, 131, and 132 as well as in the drawings at Figs. 13B, 14B, 15A, and 16A, D, and E that do not contain a SEQ ID NO. As described above, the aforementioned pages and Fig. 13B are amended to assign a SEQ ID NO to the sequences shown. In addition, the paragraphs in the specification describing Figs. 14B, 15A, and 16A, D, and E are amended to assign SEQ ID NOs to the sequences shown in these figures. In view of the foregoing amendments and remarks, Applicant submits that the application complies with 37 C.F.R. §§ 1.821-1.825. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the objection to the specification for allegedly failing to comply with the sequence requirements.

(2) Drawings

On pages 4 and 5 of the Office Action, the Examiner objects to the drawings filed on April 2, 2004 because each sequence in the drawings does not contain a SEQ ID NO. Fig. 13B has been amended to assign a SEQ ID NO to each sequence shown. Furthermore, as described above, the paragraphs in the specification that describe Figs. 14B, 15A, and 16A, D, and E have been amended to assign SEQ ID NOs to the sequence shown in these figures. Accordingly, Applicant submits that the application complies with 37 C.F.R. §§ 1.821-1.825, and respectfully requests that the Examiner reconsider and withdraw the objection to the drawings.

(3) Specification

On pages 5 and 6 of the Office Action, the Examiner objects to the specification because paragraph 0178 contains an embedded hyperlink and paragraph 0050 contains a misspelling of the world "structure." These paragraphs have been amended to remove the hyperlink and correct the typographical error. In view of the foregoing, Applicant respectfully requests that the Examiner reconsider and withdraw the objection to the specification.

2. Patentability Remarks

a. 35 U.S.C. § 101 and 112, first paragraph

On pages 3-5 of the Office Action, the Examiner rejects claims 16, 18, 19, and 21-23 under 35 U.S.C. § 101 because the claimed subject matter is allegedly not supported by either a specific and substantial asserted utility, a credible asserted utility, or a well established utility. In order to satisfy the

utility requirement, a specific and substantial utility must either (i) be cited in the specification or (ii) be recognized as well as established in the art, and the utility must be credible. *See In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005) and *Revised Interim Utility Guideline Training Materials* ("*Guidelines*").

(1) Specific Utility

A specific utility is a utility that is specific to the particular claimed subject matter, which is in contrast to a general utility that would be applicable to a broad class of inventions. *See Fisher* 421 F.3d at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a specific utility for the claimed microRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, the claims at issue were directed to five (5) out of more than 32,000 EST that were disclosed in the application. Each of disclosed ESTs were from a cDNA library of pooled leaf tissue isolated from a maize plant. The *Fisher* application did not disclose the location of the ESTs in the genome or the function of the underlying genes. *Fisher* asserted that the utilities for claimed ESTs were (1) serving as a molecular marker; (2) measuring the level of mRNA in a tissue sample; (3) provide a source of primers for PCR of specific genes; (4) identifying the presence or absence of a polymorphism; (5) isolating promoters via chromosome walking; (6) controlling protein expression; and (7) locating genetic molecules of other plants and organisms. *See Fisher*, 421 F.3d at 1367-1368. It is important to note that each of the utilities asserted were not limited to any specific gene, genetic location or protein.

The *Fisher* court concluded that the asserted utilities were clearly not "specific." The court explained that any EST transcribed from any gene in maize could perform the seven uses such as being a molecular marker, a primer, or measure the level of RNA in a tissue sample. In other words, nothing about the seven alleged uses separated the claimed ESTs from the vast number of other ESTs also disclosed in the application. The keystone to the lack of specific utility in *Fisher* is that the claimed ESTs **did not correlate to an underlying gene of known function found in the maize genome**.

Similar to *Fisher*, the current application discloses a large number of nucleic acid sequences. In stark contrast to *Fisher*, however, the instant application provides that each of the disclosed nucleic acids may be used to target and modulate expression of **specific** gene transcripts. Table 7, lines 844212-844215 and Table 8, lines 2025078-2025094 of the application disclose that the claimed microRNA-related sequences specifically target mRNA transcripts of the NP_039906.1 gene. Consequently, the claimed nucleic acids are of a **specific and unique nature** because these nucleic acids regulate the translation of mRNAs from the **specific target gene NP_039906.1**. Accordingly, the asserted utility of the claimed invention is not vague or meaningless, and there is a well-defined public benefit to regulating the NP_039906.1 gene.

(2) Substantial Utility

To satisfy the "substantial" utility requirement, an asserted use must show that the claimed invention has a significant and presently available benefit to the public. *See Id.* at 1371 and *Guidelines*. Applicant respectfully submits that the application provides a substantial utility for the claimed microRNA-related nucleic acids in accordance with *Fisher* and *Guidelines*.

In *Fisher*, it was admitted that the underlying genes for the ESTs had no known function. *Fisher* argued that this was irrelevant because the seven asserted uses (discussed above) were not related to the function of the underlying genes. Importantly, *Fisher* failed to provide any evidence that any of the claimed ESTs could be used for any of the asserted uses. Consequently, the *Fisher* court concluded that the claimed ESTs were "mere 'objects of use-testing,' to wit, objects upon which scientific research could be performed with no assurance that anything useful will be discovered in the end." *See Fisher*, 421 F.3d at 1373, quoting *Brenner v. Manson*, 383 U.S. 519 (1966).

In further sharp contrast to *Fisher*, the present application discloses that the claimed nucleic acids may be used to bind and regulate mRNA transcripts of the NP_039906.1 gene of Epstein-Barr virus (EBV). *Instant Application*, Table 8, lines 2025078-2025094. In addition, ebv-miR-BART3 is known to be expressed and upregulated during EBV lytic replication, and this microRNA may play a particularly important role during EBV infection of epithelial cells. Cai X, *et al.*, *PLoS Pathogens* 2006;2(3):236-47 ("Cai"). Accordingly, ebv-miR-BART3 expression could be modulated *in vitro* to affect viral titer during EBV lytic replication.

The evidence described above clearly supports that the claimed nucleic acids have a number of presently available benefits to the public. Such benefits are the ability to modulate the expression of NP_039906.1 in order to alter EBV viral titer during its' lytic replication cycle. In view of the application providing particular targets of known function for the claimed microRNA-related nucleic acids, Applicant respectfully submits that the specific and substantial utility requirements are satisfied in accordance of *Fisher* and *Guidelines*.

(3) Credible Utility

An asserted utility is credible if the assertion is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided. An assertion is credible unless (i) the logic underlying the assertion is seriously flawed, or (ii) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Accordingly, the invention must be operable to achieve useful results. *See Guidelines* at page 5 and *In re Swartz*, 232 F.3d 862 (Fed. Cir. 2000). The proper inquiry for determining credible utility is whether a person of ordinary skill in the art would conclude that the asserted utility is more likely true than not. Applicant respectfully submits that the

record clearly shows that one of ordinary skill in the art would believe that the claimed nucleic acids may be used to modulate expression of the specific mRNA targets.

Dr. Yitzhak Pilpel, who is an expert in the field of microRNA and RNAi biology, states in the attached declaration (Appendix) that the claimed nucleic acids would likely inhibit expression of NP_039906.1 mRNA transcripts. Dr. Pilpel's opinion is based on a number of facts.

(a) Characteristics of microRNA-target mRNA binding

Dr. Pilpel states that researchers in the microRNA field believed that there are a number of characteristics of inhibition of protein expression via target mRNA interference by an endogenous or synthetic nucleic acid of 18-25 nucleotides in length, such as a microRNA. For example, the 5' end of the microRNA may contain a "seed" that is full complementary between the first 1-8 base pairs of the 5' of the microRNA and the target mRNA. *See* ¶¶ 2 and 3, Pilpel Declaration. This seed may be conserved and is often flanked by adenosine. *See* ¶ 3, Pilpel Declaration. If there is insufficient base-pairing of the microRNA 5' seed there may be compensatory complementation at the 3' end of a microRNA and its target mRNA sequence. *See* ¶ 3, Pilpel Declaration. Finally, although not obligatory, there may be multiple binding sites for a microRNA on a mRNA target, which may enhance the binding effect of target repression. *See* ¶ 3, Pilpel Declaration.

Importantly, Dr. Pilpel states that the claimed nucleic acid sequence as set forth in SEQ ID NO: 14051 and its respective target gene sequences of NP_039906.1 (as depicted in column B, row 2, p. 5, Table A) are consistent with the characteristics of the microRNA:target mRNA binding described above. *See* ¶ 6, Pilpel Declaration. In view of these conserved characteristics, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 14051 (column B, row 2, p. 5, Table A) is likely to inhibit expression of the protein encoded by the target gene NP_039906.1 in view of the characteristics of microRNA:mRNA binding properties. *See* ¶ 6, Pilpel Declaration.

(b) MicroRNA algorithms

Dr. Pilpel states several effective microRNA:target algorithms have been based upon the characteristics of microRNA:target mRNA binding described above. *See* ¶ 4, Pilpel Declaration. Dr. Pilpel provides TargetScan (developed by Lewis *et al., Cell* 115:787-798 (2003)) and miRanda (developed by Enright *et al.*, *Genome Biology* 5:R1 (2003)) as examples of such algorithms. The TargetScan algorithm predicted 15 targets of various miRNAs identified by Lewis, and 11 of the predicted interactions between a particular miRNA and target mRNA were biologically validated with a false positive rate between 22 and 31%. The miRanda algorithm was also an effective microRNA:target algorithm, where 9 out of 10 predicted targets identified by the miRanda algorithm in Enright were biologically validated with a 24-39% false positive rate. *See* ¶ 4, Pilpel Declaration. MicroRNA:target

interactions were also further validated by virtue of target binding site conservation among multiple organisms. *See* ¶ 5, Pilpel Declaration.

Importantly Dr. Pilpel states that SEQ ID NO: 14051 and its respective target gene sequences of NP_039906.1 are consistent with microRNA and target mRNAs predicted by the algorithms described above. *See* ¶¶ 4 and 5, Pilpel Declaration. In view of these facts, Dr. Pilpel concludes that the microRNA of SEQ ID NO: 14051 is likely to inhibit expression of the protein where co-expressed. See ¶ 6, Pilpel Declaration. Moreover, Cai establishes that ebv-miR-BART3 (SEQ ID NO: 14051) is expressed during EBV infection, and in particular is upregulated during the lytic stage of viral replication.

(c) NP_039906.1

Applicant further submits that NP_039906.1 is a credible target for trans-acting regulatory elements. Specifically, the Pilpel Declaration indicates that the claimed nucleic acids are capable of binding NP_039906.1 with 16 out of 24 nucleotides of complementarity, as demonstrated at Table 7, lines 844212-844215 and Table 8, lines 2025078-2025094 of the specification, and as shown below.

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                          ---          GA GTTG       -
NP_039906.1           5'      CCTGGTGA   A     GTGGTG G 3'
SEQ ID NO: 14051      3'      GGACCACT   T     CACCAC C 5'
                          TGT          GA ----       G
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In view of the foregoing, Applicant asserts that a person of ordinary skill in the art would more than likely conclude that the claimed nucleic acids may be used to modulate expression of the NP_039906.1 transcript, which in turn may respectively alter EBV viral titer during its' lytic replication cycle. Accordingly, a proper credible utility is asserted for the claimed nucleic acids. Applicant respectfully asserts that a specific and substantial utility has been demonstrated both in the specification and by what was recognized as well as established in the art at the time of filing, and the utility is credible. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 101.

b. 35 U.S.C. § 112

(1) 35 U.S.C. § 112, Second Paragraph

On pages 15-17 of the Office Action, the Examiner rejects claims 16, 18, 19, and 21-23 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite.

"comprising"

On page 16, the Examiner asserts that claim 16 improperly contains the term "comprising" instead of "consisting of." Applicant respectfully disagrees. Nevertheless, amended claim 16 recites a Markush group.

"the at least Y nucleotides"

On page 16, the Examiner asserts that the limitation "the at least Y nucleotides" of claim 18 has insufficient antecedent basis. Applicant respectfully disagrees. Nevertheless, amended claim 18 does not recite this limitation.

"an RNA equivalent"

On page 17, the Examiner rejects claim 16 because the scope and meaning of the limitation "an RNA equivalent of (a)" is allegedly unclear. The Examiner asserts that it is not understood what is meant by this limitation because SEQ ID NO: 399738 is a RNA sequence. Amended claim 16 recites "a DNA encoding the sequence of (a)." Applicant submits that one of skill would instantly recognize that DNA encodes RNA.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 16, 18, 19, and 21-23 under 35 U.S.C. § 112, second paragraph.

(2) 35 U.S.C. § 112, First Paragraph

On pages 15 and 17-20 of the Office Action, the Examiner rejects claims 16, 18, 19, and 21-24 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement.

(a) In view of alleged lack of utility

On page 15, the Examiner asserts that because the claimed subject matter lacks either a specific, substantial, and credible utility or a well-established utility, the specification also does not provide an enabling disclosure. Applicant disagrees. In view of the claimed subject matter having credible, specific, and substantial utility as described above, Applicant submits that the specification enables the claimed subject matter and respectfully requests that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

(b) In view of alleged new matter

On pages 17-20 of the Office Action, the Examiner rejects claims 16, 18, 19, and 21-23 for allegedly containing new matter.

19-140 nucleotides

On page 18, the Examiner asserts that the length limitation of 19-140 nucleotides is not supported in the application. Applicant respectfully disagrees. Nevertheless, amended claim 16 does not recite this limitation.

a sequence at least 80% identical

On pages 18 and 19, the Examiner asserts that the application lacks support for a nucleic acid being at least 80% identical to at least 19 consecutive nucleotides of SEQ ID NO: 399738 or an RNA

equivalent thereof. Applicant respectfully disagrees. Nevertheless, amended claim 16 does not recite the limitations of at least 19 consecutive nucleotides of SEQ ID NO: 399738 or of a "RNA equivalent" thereof.

complement of RNA equivalent and vector and probe comprising a RNA equivalent

On page 19, the Examiner asserts that support for "an RNA equivalent" of claim 16 cannot be located in the application. The Examiner also asserts that there is no support in the application for a complement of a RNA equivalent. On pages 19 and 20, the Examiner further asserts that the specification does not provide support for the vector or probe comprising a RNA equivalent recited in claims 22, 23, 31, and 32.

Applicant respectfully disagrees. Applicant submits that one of skill would clearly recognize that a nucleic acid sequence inherently discloses both a RNA and a DNA sequence, since DNA encodes RNA. Additionally, one of skill would understand that in light of the double-stranded nature of nucleic acids and their ability to pair, the sequence of one strand of a nucleic acid inherently discloses its complement. Nevertheless, amended claim 16 does not recite the limitation "RNA equivalent," and thus the claims also do not recite a complement of "an RNA equivalent," or a vector or a probe comprising "an RNA equivalent."

X=Y

On page 19, the Examiner asserts that there is no support in the application for the limitation "X=Y" of claim 19. Applicant respectfully disagrees. Nevertheless, amended claim 19 does not recite this limitation.

method for detecting a nucleic acid

On page 20, the Examiner asserts that the specification does not provide support for a method for detecting a nucleic acid as recited in claim 24. Applicant respectfully disagrees. Nevertheless, claim 24 is canceled without prejudice, thereby rendering moot the Examiner's rejection.

In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. § 112, first paragraph.

c. 35 U.S.C. § 102

On page 21 of the Office Action, the Examiner rejects claims 16 and 22 under 35 U.S.C. § 102(b) as allegedly being anticipated by Edwards *et al.* (US 5,578,444) ("Edwards"). The Examiner asserts that Edwards teaches SEQ ID NO: 541, which is an isolated nucleic acid sequence consisting of 50 nucleotides wherein the sequence comprises the complement of a sequence that is approximately 90.48% identical to 21 consecutive nucleotides of instant SEQ ID NO: 399738.

Amended claim 16 is related to sequences related to SEQ ID NOs: 399404, 399423, 433424, 399427, 399441, 14005, 14011, 14020, 14039, 14046, and 14051 (which are contained within SEQ ID

NO: 399738), and sequences at least 80% identical thereto. Applicant submits that Edwards does not teach or suggest a sequence that is related to SEQ ID NOs: 399404, 399423, 433424, 399427, 399441, 14005, 14011, 14020, 14039, 14046, or 14051, or a sequence at least 80% identical thereto. Accordingly, Edwards does not anticipate the instant claims. In view of the foregoing amendments and remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 16 and 22 under 35 U.S.C. § 102b.

d. Double Patenting

On pages 22 and 23 of the Office Action, the Examiner provisionally rejects claims 16 and 19 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claim 1 of copending U.S. App. No. 11/511,035. Applicant notes that the instant application was filed prior to the cited application. In view of the remarks made herein and pursuant to MPEP 804.I.B.1., Applicant believes that the only outstanding rejection in the instant application is the obviousness-type double patenting rejection, which allows the Examiner to withdraw the provisional double patenting rejection in the instant application and reject co-pending U.S. Appl. No. 11/511,035 under nonstatutory obviousness-type double patenting.

On page 23, the Examiner provisionally rejects claims 16, 18, 19, and 21-23 on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 1-3 and 8 of copending U.S. App. No. 10/605,838. Applicant respectfully requests that the Examiner hold this rejection in abeyance until there is allowable subject matter, at which time, the Applicant will consider amending the claims in U.S. Pat. App. No. 10/605,838, or filing a terminal disclaimer.

On pages 23 and 24, the Examiner provisionally rejects the instant claims on the ground of obviousness-type double patenting over various cited patent applications. Applicant respectfully requests that the Examiner hold the rejection in abeyance until there is allowable subject matter, at which time the rejection may be withdrawn from the instant application and applied to any later-filed application and/or Applicant will consider amending the claims in any earlier filed applications or filing a terminal disclaimer.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

POLSINELLI SHALTON FLANIGAN SUELTHAUS PC

Dated: May 21, 2008

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